ORIGINAL ARTICLE

Stress Ulcer Prophylaxis during Invasive Mechanical Ventilation

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ABSTRACT

BACKGROUND

Whether proton-pump inhibitors are beneficial or harmful for stress ulcer prophylaxis in critically ill patients undergoing invasive ventilation is unclear.

METHODS

In this international, randomized trial, we assigned critically ill adults who were undergoing invasive ventilation to receive intravenous pantoprazole (at a dose of 40 mg daily) or matching placebo. The primary efficacy outcome was clinically important upper gastrointestinal bleeding in the intensive care unit (ICU) at 90 days, and the primary safety outcome was death from any cause at 90 days. Multiplicity-adjusted key secondary outcomes were ventilator-associated pneumonia, *Clostridioides difficile* infection, and patient-important bleeding.

RESULTS

A total of 4821 patients underwent randomization in 68 ICUs. Clinically important upper gastrointestinal bleeding occurred in 25 of 2385 patients (1.0%) receiving pantoprazole and in 84 of 2377 patients (3.5%) receiving placebo (hazard ratio, 0.30; 95% confidence interval [CI], 0.19 to 0.47; P<0.001). At 90 days, death was reported in 696 of 2390 patients (29.1%) in the pantoprazole group and in 734 of 2379 patients (30.9%) in the placebo group (hazard ratio, 0.94; 95% CI, 0.85 to 1.04; P=0.25). Patient-important bleeding was reduced with pantoprazole; all other key secondary outcomes were similar in the two groups.

CONCLUSIONS

Among patients undergoing invasive ventilation, pantoprazole resulted in a significantly lower risk of clinically important upper gastrointestinal bleeding than placebo, with no significant effect on mortality. (Funded by the Canadian Institutes of Health Research and others; REVISE ClinicalTrials.gov number, NCT03374800.)

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*A complete list of the investigators in the REVISE trial is provided in the Supplementary Appendix, available at NEJM.org.

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SHOUT
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Critically ill patients are at risk for stress-induced gastrointestinal ulceration, which may cause upper gastrointestinal bleeding.[1,2] Consequently, patients in the intensive care unit (ICU) typically receive acid suppression to prevent gastrointestinal bleeding,[3] most commonly a proton-pump inhibitor.[4-6] In a recent blinded trial, investigators found that pantoprazole lowered the risk of clinically important upper gastrointestinal bleeding as compared with placebo but increased the risk of death in the subgroup of patients with the most severe illness.[7] An open-label, cluster-randomized trial showed fewer gastrointestinal bleeding episodes during treatment periods with proton-pump inhibitors as compared with histamine 2–receptor antagonists[8] and also suggested an increased risk of death in the subgroup of the most severely ill patients assigned to receive proton-pump inhibitors.

A network meta-analysis that summarized all evidence from randomized trials showed that acid suppression reduced the risk of upper gastrointestinal bleeding among patients in the ICU but had no effect on mortality for any prophylactic agent.[9] However, harm with proton-pump inhibitors could not be ruled out regarding the risks of health care–associated pneumonia and *Clostridioides difficile* infection.[9] Accordingly, recent guidelines have issued only weak recommendations for stress ulcer prophylaxis, especially with proton-pump inhibitors, in critically ill patients at high risk for bleeding and particularly in those with sepsis[10] on the basis of moderate-quality evidence.[11] After conducting pilot trials,[12,13] we began enrolling patients in the Reevaluating the Inhibition of Stress Erosions (REVISE) trial to address this clinical question.

Methods

Trial Design and Oversight

This investigator-initiated, multicenter, randomized, blinded trial was conducted at 68 hospitals in Australia, Brazil, Canada, England, Kuwait, Pakistan, Saudi Arabia, and the United States. Canadian and Australian peer-review granting organizations (including the Canadian Institutes of Health Research and the National Health and Medical Research Council of Australia) funded the trial. There was no commercial involvement. Methods centers at McMaster University and the George Institute for Global Health coordinated the trial and conducted regional data monitoring. McMaster University performed biannual central monitoring. A data and safety monitoring committee independently reviewed safety and efficacy at interim analyses. The protocol[14] (available with the full text of this article at NEJM.org) and statistical analysis plan[15] have been published previously; protocol amendments were approved by research ethics committees and regulators at the participating hospitals. Details are provided in the Supplementary Appendix (available at NEJM.org). Enrollment was paused during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic for the shortest possible periods at each center, which allowed for the enrollment of these patients without protocol modification.[16]

The trial was endorsed by the Canadian Critical Care Clinical Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group. The investigators at the participating sites vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Patients

Eligible adults (≥18 years of age) were undergoing invasive mechanical ventilation in the ICU, and such treatment was expected to continue beyond the calendar day after randomization. Patients were excluded if invasive ventilation had been initiated at least 72 hours before randomization, if they had received more than one daily-dose equivalent of acid suppression in the ICU, or if acid suppression was specifically indicated or contraindicated. Inclusion and exclusion criteria are detailed in Table S1 in the Supplementary Appendix. Eligible patients were enrolled with a priori informed consent, by consent-to-continue (deferred consent), or an opt-out model, as approved by local review boards.[14]

Randomization and Intervention

Research staff members used a password-protected website to perform randomization with the use of permuted blocks of undisclosed variable size. Patients were assigned in a 1:1 ratio to receive either intravenous pantoprazole or placebo, with stratification according to trial center and prehospital receipt of acid suppression. Trial pharmacists or staff members who were aware of

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the trial-group assignments prepared the regionally sourced pantoprazole (at a dose of 40 mg reconstituted with 0.9% sodium chloride) or matching placebo (0.9% sodium chloride). To ensure blinding, we verified the color stability of pantoprazole and placebo during a 10-day period.[17]

Pantoprazole or placebo was administered by bedside staff members in a blinded manner for 90 days or until the discontinuation of invasive ventilation, the occurrence of a prespecified clinical indication or contraindication to proton-pump inhibitors, or death, whichever came first. Pantoprazole or placebo was resumed if invasive ventilation was reinstituted during the index ICU admission. Other interventions were performed at the discretion of treating clinicians. Trial-group assignments remained blinded to the patients, their families, clinical and research staff members, outcome adjudicators, and biostatisticians until the completion of data analysis.

DATA COLLECTION

Training with respect to protocol implementation was designed to align with the International Council for Harmonisation guidelines for Good Clinical Practice and other locally applicable regulations. Research staff members recorded the patients' characteristics (e.g., demographic and life-support features) at baseline, collected trial data on a daily basis, and recorded clinical outcomes by entering deidentified data in a secure electronic data-capture system (iDataFax). If patients had suspected clinically important upper gastrointestinal bleeding, relevant anonymized clinical, laboratory, and procedural source data were submitted to the trial methods centers.

OUTCOMES

The primary efficacy outcome was clinically important upper gastrointestinal bleeding, identified locally as overt gastrointestinal bleeding with evidence of hemodynamic compromise or leading to therapeutic interventions in the ICU (or resulted in readmission to the ICU during the index hospital stay) up to 90 days after randomization.[14] Two trained physicians who were unaware of trial-group assignments and trial centers adjudicated all bleeding events to determine whether the primary-outcome definition had been fulfilled. Discrepancies were resolved by discussion with a third adjudicator who was also unaware of trial-group assignments and centers. Details regarding adjudication methods are provided in Table S3 and have been published previously.[18]

The primary safety outcome was death from any cause at 90 days. For patients who were discharged from the hospital before 90 days, their current health status was ascertained by contact with the patients or their families at home or from medical records.

Secondary outcomes were ventilator-associated pneumonia, *C. difficile* infection in hospital, initiation of renal-replacement therapy, ICU and hospital mortality, and patient-important upper gastrointestinal bleeding. We defined patient-important bleeding on the basis of the results of a mixed-methods study involving ICU survivors and their families.[19] In this study, the participants considered bleeding to be important if it required a single blood transfusion, vasopressor treatment, diagnostic endoscopy, computed tomographic angiography, or surgery or if it resulted in death, disability, or prolonged hospitalization.[20]

Tertiary outcomes were the total number of units of red-cell transfusions, peak serum creatinine levels, duration of mechanical ventilation, and length of stay in the hospital and ICU. Serious adverse events that were prespecified trial outcomes were not separately reported, according to guidance for investigator-initiated trials of commonly prescribed drugs in the ICU.[21]

STATISTICAL ANALYSIS

We determined that the enrollment of 4800 patients would provide the trial with 85% power to detect an absolute between-group difference of 1.5 percentage points in the primary efficacy outcome, according to a baseline risk of 3% in the placebo group and a two-sided type I error of 0.05.[14,15] Patients were evaluated in the group to which they had been assigned. We performed Cox proportional-hazards analysis for the primary efficacy and safety outcomes after adjustment for receipt of prehospital acid suppression. This analysis was used to calculate hazard ratios and 95% confidence intervals, along with absolute risk differences and Kaplan–Meier curves. Mortality outcomes were also adjusted for baseline illness severity as measured by the Acute Physiology and Chronic Health Evaluation (APACHE) II score, which ranges from 0 to 71, with higher scores indicating an increased risk of death. Cox proportional-hazards analysis was also used for

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the evaluation of dichotomous secondary outcomes. Skewed continuous secondary outcomes were log-transformed; if the data were normally distributed, parametric methods were used. If outcome distributions remained skewed after log-transformation, nonparametric methods were used. Graphical approaches were used to examine residuals to assess model assumptions and goodness-of-fit testing, including the proportional-hazards assumption for Cox regression. For red-cell transfusions, we compared groups using negative binomial regression. For all other continuous outcomes, we used linear regression on the original scale or on the log scale after adjustment for prehospital acid suppression or the Wilcoxon rank-sum test. Because data were missing for less than 2% of patients for continuous outcomes, multiple imputations were not performed as prespecified.[15] The reported denominators represent the number of patients for whom full follow-up data were available for each outcome. For time-to-event analyses, data for patients with incomplete follow-up were censored at the last follow-up.

For the primary efficacy and safety outcomes, we performed analyses of subgroups that had prespecified hypotheses.[15] These analyses included evaluations of prehospital receipt of acid suppression as compared with none, an APACHE II score of 25 or more as compared with a score of less than 25, ICU admission for medical as compared with surgical or trauma diagnoses, positive as compared with negative SARS-CoV-2 status, and female as compared with male sex.

Prespecified sensitivity analyses for the primary efficacy and safety outcomes were an analysis without adjustment for prehospital acid suppression, an analysis that included the trial center as a random effect, analysis restricted to patients who had received either pantoprazole or placebo for at least 80% of trial days during invasive ventilation, and competing-risk analysis for the primary efficacy outcome[22] with death as the competing risk.[23] In our analyses of secondary and tertiary outcomes, along with subgroups, we used the sequential Holm–Šidák approach to adjust for multiple significance testing.[24,25]

The data and safety monitoring committee independently reviewed blinded interim analyses, with no stopping guides for futility and with conservative warning guides for benefit. The committee advised the continuation of the trial after the examination of 90-day mortality data for 1200 patients. We conducted one interim analysis of data involving 2400 patients, using two-sided tests with a fixed conservative alpha level of 0.001 and an alpha level of 0.05 for the final analyses.[26,27] All analyses were performed with the use of SAS software, version 9.4. After reviewing all outcomes, the committee advised continuation of the trial.

RESULTS

PATIENTS

Patients were enrolled from July 9, 2019, to October 30, 2023. Of the 4821 patients who were included in the analyses, 2417 were randomly assigned to the pantoprazole group and 2404 to the placebo group (Fig. 1). At the time of this trial, 1719 of the patients (35.7%) were coenrolled in another study, primarily in randomized trials (87.4% of those who were coenrolled), with patients evenly distributed between the pantoprazole group and the placebo group (Table S14). Data regarding 90-day vital status were collected for 4769 patients (98.9%).

At baseline, the characteristics of the patients were similar in the two groups (Table 1). The mean (±SD) age was 58.2±16.4 years, the mean APACHE II score was 21.7±8.3, and 1752 patients (36.3%) were female. At baseline, all the patients were receiving invasive mechanical ventilation, 3389 (70.3%) were receiving inotropes or vasopressors, and 308 (6.4%) were receiving renal-replacement therapy. In the two groups, the patients had similar frequencies of prehospital acid suppression (in 1120 patients, 23.2%) and glucocorticoid therapy (in 1694 patients, 35.1%). Cointerventions in the two groups are provided in Table S4.

Pantoprazole or placebo was administered for a median of 5 days (interquartile range, 3 to 10). A total of 4699 patients (97.5%) received their assigned agent or had a prespecified exemption for at least 80% of days of invasive ventilation. There were no requests for unblinding of the trial-group assignments. Details regarding fidelity to the trial protocol and reasons for nonadministration of pantoprazole or placebo are provided in Table S5.

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PRIMARY EFFICACY OUTCOME

Clinically important upper gastrointestinal bleeding occurred in 25 of 2385 patients (1.0%) receiving pantoprazole and in 84 of 2377 patients (3.5%) receiving placebo (hazard ratio, 0.30; 95% confidence interval [CI], 0.19 to 0.47; P<0.001), for an absolute difference of 2.5 percentage points (95% CI, 1.6 to 3.3) (Table 2 and Fig. S1A).

Details regarding the presentation of bleeding, qualifying criteria for the definition of the primary efficacy outcome, and endoscopic findings are provided in Table S6. Most bleeding episodes fulfilled the definition according to the criteria of a decrease of at least 2 g per deciliter of hemoglobin within 24 hours after the identification of a bleeding episode, the transfusion of at least 2 units of packed red cells within 24 hours after the identification, hypotension or the initiation of a vasopressor or an inotrope, or the performance of an invasive therapeutic intervention.

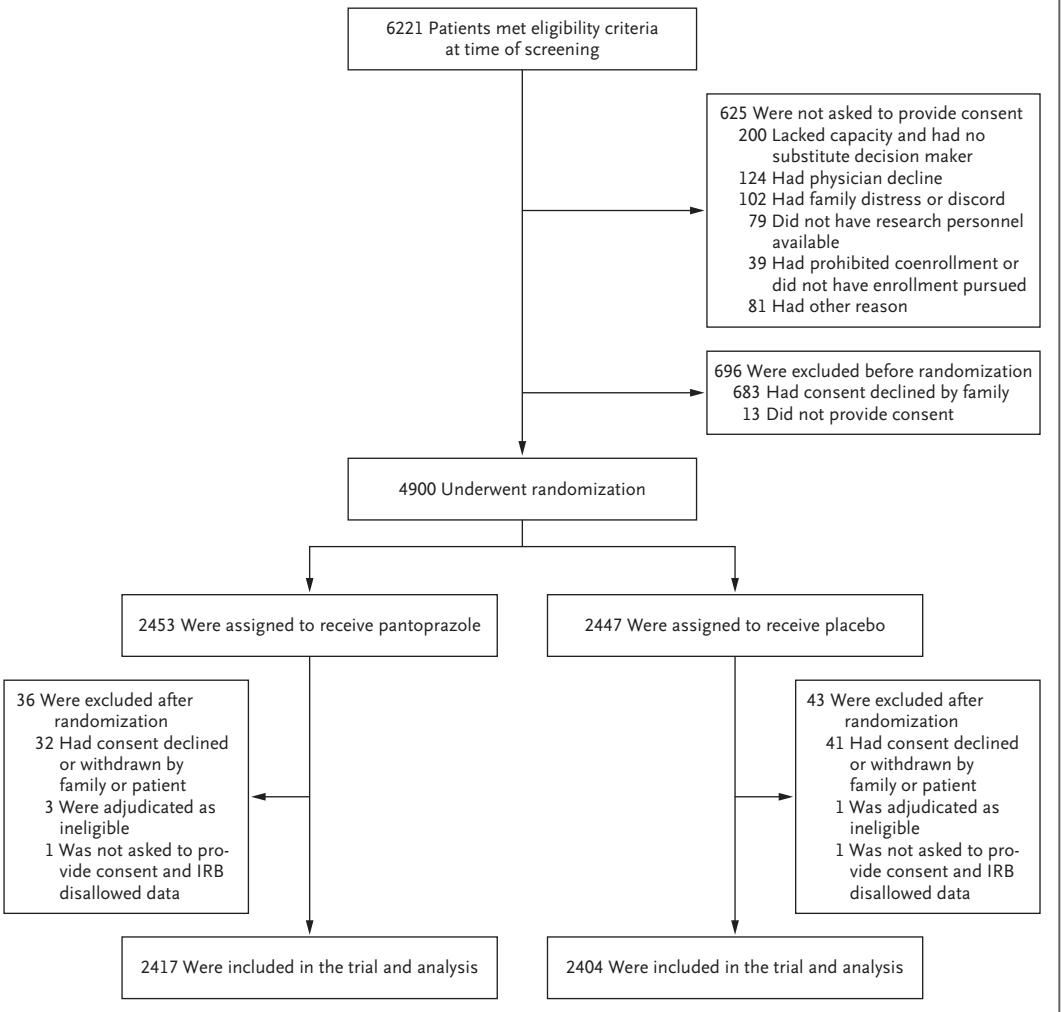
6221 Patients met eligibility criteria at time of screening
625 Were not asked to provide consent
200 Lacked capacity and had no substitute decision maker
124 Had physician decline
102 Had family distress or discord
79 Did not have research personnel available
39 Had prohibited coenrollment or did not have enrollment pursued
81 Had other reason
696 Were excluded before randomization
683 Had consent declined by family
13 Did not provide consent
4900 Underwent randomization
2453 Were assigned to receive pantoprazole
2447 Were assigned to receive placebo
36 Were excluded after randomization
32 Had consent declined or withdrawn by family or patient
3 Were adjudicated as ineligible
1 Was not asked to provide consent and IRB disallowed data
43 Were excluded after randomization
41 Had consent declined or withdrawn by family or patient
1 Was adjudicated as ineligible
1 Was not asked to provide consent and IRB disallowed data
2417 Were included in the trial and analysis
2404 Were included in the trial and analysis

Figure 1. Enrollment and Randomization.

Shown is the screening process, selection, and flow of patients through the trial. Patients may not have been asked to provide consent because they had been enrolled in an additional study in which coenrollment was not allowed. Other reasons for nonprovision of consent include lack of national residence, incarceration, and a language barrier in the absence of a valid interpreter. Reasons for postrandomization exclusion include breast-feeding, a lack of endotracheal intubation, and previous enrollment in the REVISE trial. IRB denotes institutional review board.

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Pantoprazole (N=2417)	Placebo (N=2404)
Age — yr	58.2±16.4	58.3±16.4
APACHE II score†	21.8±8.4	21.7±8.2
Sex — no. (%)		
Female	883 (36.5)	870 (36.2)
Male	1534 (63.5)	1534 (63.8)
Patient status — no. (%)		
Medical	1753 (72.5)	1767 (73.5)
Surgical	295 (12.2)	325 (13.5)
Trauma	369 (15.3)	312 (13.0)
Admitting diagnostic category — no. (%)		
Cardiovascular	231 (9.6)	252 (10.5)
Respiratory	752 (31.1)	768 (31.9)
Gastrointestinal	108 (4.5)	109 (4.5)
Neurologic	527 (21.8)	554 (23.0)
Sepsis	200 (8.3)	199 (8.3)
Trauma	369 (15.3)	312 (13.0)
Metabolic	101 (4.2)	90 (3.7)
Renal	33 (1.4)	31 (1.3)
Other medical	39 (1.6)	31 (1.3)
Other surgical	57 (2.4)	58 (2.4)
Acid suppression before hospitalization — no. (%)		
No acid suppression before hospitalization	1847 (76.4)	1854 (77.1)
Proton-pump inhibitor and H2RA	3 (0.1)	2 (0.1)
Proton-pump inhibitor only	548 (22.7)	536 (22.3)
H2RA only	14 (0.6)	10 (0.4)
Drug class not available	5 (0.2)	2 (0.1)
Glucocorticoid ≥1 wk before randomization — no. (%)‡	856 (35.4)	838 (34.9)
Type of life support — no. (%)		
Invasive mechanical ventilation	2417 (100)	2404 (100)
Inotrope or vasopressor infusion	1680 (69.5)	1709 (71.1)
Renal-replacement therapy	153 (6.3)	155 (6.4)

* Plus–minus values are means ±SD. H2RA denotes histamine 2–receptor antagonist.
† Scores on the APACHE (Acute Physiology and Chronic Health Evaluation) II range from 0 to 71, with higher scores representing more severe disease and a higher risk of death. The APACHE II score is calculated on the basis of 12 physiologic variables that include the patient's age and long-term health status.
‡ Glucocorticoids could have been prescribed for any reason in an oral or intravenous formula.

The percentage of agreement among adjudicators of clinically important upper gastrointestinal bleeding was 98.7% (in 233 of 236 patients reviewed).

PRIMARY SAFETY OUTCOME

Death by 90 days after randomization was reported in 696 of 2390 patients (29.1%) in the pantoprazole group and in 734 of 2379 patients (30.9%) in the

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Table 2. Primary Efficacy and Safety Outcomes.

Outcome	Pantoprazole (N=2417)	Placebo (N=2404)	Absolute Difference (95% CI)	Hazard Ratio (95% CI)*	P Value
	no./total no. (%)		*percentage points*		
Primary efficacy outcome: clinically important upper gastrointestinal bleeding	25/2385 (1.0)	84/2377 (3.5)	2.5 (1.6 to 3.3)	0.30 (0.19 to 0.47)	<0.001
Primary safety outcome: 90-day mortality	696/2390 (29.1)	734/2379 (30.9)	1.7 (−0.9 to 4.3)	0.94 (0.85 to 1.04)	0.25

* Hazard ratios were adjusted for prehospital use of histamine 2–receptor antagonists or proton-pump inhibitors. Mortality analyses were also adjusted for the baseline APACHE II score.

placebo group (hazard ratio, 0.94; 95% CI, 0.85 to 1.04; P=0.25). These findings resulted in an absolute between-group difference of 1.7 percentage points (95% CI, −0.9 to 4.3) (Table 2 and Fig. S1B).

PRESPECIFIED SUBGROUP AND SENSITIVITY ANALYSES

Subgroup analyses did not suggest an effect modification of pantoprazole on primary efficacy or safety outcomes on the basis of the prespecified subgroup comparisons (prehospital acid suppression vs. none, APACHE II score of ≥25 vs. <25, medical vs. surgical or trauma ICU admission, positive vs. negative status for SARS-CoV-2, and female vs. male sex) (Fig. 2A and 2B and Table S7). We did not apply criteria to assess subgroup credibility[28] because all multiplicity-adjusted P values were above 0.10, according to our statistical analysis plan.[15] Sensitivity analyses yielded results that were similar to those in the main analyses (Table S8).

SECONDARY OUTCOMES

Ventilator-associated pneumonia occurred in 556 of 2394 patients (23.2%) in the pantoprazole group and in 567 of 2381 patients (23.8%) in the placebo group (Table 3). We did not find material differences between the groups using alternative pneumonia definitions (Table S9). *C. difficile* infection occurred in 28 of 2385 patients (1.2%) receiving pantoprazole and in 16 of 2377 patients (0.7%) receiving placebo; associated severity is shown in Table S10.

Patient-important gastrointestinal bleeding occurred less often in the pantoprazole group than in the placebo group (in 36 of 2385 patients [1.5%] vs. 100 of 2377 patients [4.2%]; hazard ratio, 0.36; 95% CI, 0.25 to 0.53; P<0.001). The presentation of bleeding, qualifying criteria that were fulfilled for this outcome, and endoscopic findings are provided in Table S11.

Other secondary outcomes were similar in the two groups. Death in the ICU was reported in 488 of 2402 patients (20.3%) in the pantoprazole group and in 515 of 2392 patients (21.5%) in the placebo group (hazard ratio, 0.98; 95% CI, 0.87 to 1.11; P=0.94). Death in the hospital occurred in 630 of 2399 patients (26.3%) in the pantoprazole group and in 677 of 2381 patients (28.4%) in the placebo group (hazard ratio, 0.96; 95% CI, 0.86 to 1.07; P=0.91).

TERTIARY OUTCOMES AND ADVERSE EVENTS

No material between-group differences occurred in any tertiary outcomes, including the total number of units of transfused red cells and the peak serum creatinine level in the ICU. Patients underwent invasive mechanical ventilation for a median of 6 days (interquartile range, 3 to 11) in the two groups. In the two groups, the durations of ICU stay (median, 10 days; interquartile range, 6 to 16) and hospital stay (median, 20 days; interquartile range, 11 to 37) were similar (Table 3). With the exclusion of events that were included in the trial outcomes, one adverse drug reaction and one suspected serious adverse reaction were reported in the placebo group (Table S12).

DISCUSSION

In this trial involving patients undergoing invasive mechanical ventilation, intravenous pantoprazole reduced the risk of clinically important

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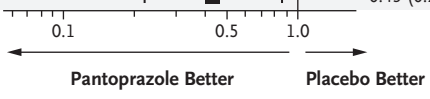
upper gastrointestinal bleeding but did not affect mortality. We also documented a lower risk of patient-important upper gastrointestinal bleeding (as determined from the responses of ICU survivors and their families in a previous trial) among the patients who were receiving pantoprazole. We did not find that patients in the pantoprazole group had a greater risk of ventilator-associated pneumonia or *C. difficile* infection than those in the placebo group. Also similar in the two groups

A Clinically Important Upper Gastrointestinal Bleeding

Subgroup	Pantoprazole	Placebo	Hazard Ratio (95% CI)	P Value
	no. of patients with event/total no.			
Use of acid suppression before hospitalization				0.91
No	18/1822	63/1829	0.30 (0.18–0.51)	
Yes	7/563	21/548	0.29 (0.12–0.68)	
APACHE II score				0.12
<25	15/1570	30/1582	0.51 (0.28–0.96)	
≥25	10/815	54/795	0.18 (0.09–0.35)	
Diagnosis on ICU admission				0.75
Surgical or trauma	4/651	20/630	0.20 (0.07–0.57)	
Medical	21/1734	64/1747	0.33 (0.20–0.55)	
SARS-CoV-2 status				0.98
No active infection	21/2145	71/2145	0.30 (0.18–0.48)	
Active infection	4/240	13/232	0.33 (0.11–1.01)	
Sex				0.55
Male	13/1513	56/1519	0.23 (0.13–0.43)	
Female	12/872	28/858	0.43 (0.22–0.85)	



B 90-Day Mortality

Subgroup	Pantoprazole	Placebo	Hazard Ratio (95% CI)	P Value
	no. of patients with event/total no.			
Use of acid suppression before hospitalization				0.97
No	491/1823	524/1835	0.95 (0.84–1.07)	
Yes	205/567	210/544	0.92 (0.76–1.12)	
APACHE II score				0.27
<25	338/1574	391/1579	0.85 (0.74–0.98)	
≥25	358/816	343/800	1.04 (0.89–1.20)	
Diagnosis on ICU admission				0.99
Surgical or trauma	131/653	139/633	0.92 (0.72–1.17)	
Medical	565/1737	595/1746	0.95 (0.85–1.07)	
SARS-CoV-2 status				0.90
No active infection	613/2150	643/2149	0.95 (0.85–1.06)	
Active infection	83/240	91/230	0.93 (0.69–1.26)	
Sex				0.93
Male	436/1516	469/1522	0.92 (0.80–1.04)	
Female	260/874	265/857	0.99 (0.83–1.17)	

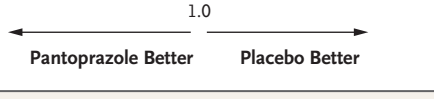


Figure 2. Primary Efficacy and Safety Outcomes in Subgroups.

Shown are subgroup analyses showing the effect of pantoprazole as compared with placebo on the primary efficacy outcome of clinically important upper gastrointestinal bleeding (Panel A) and the primary safety outcome of 90-day mortality (Panel B). Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating an increased risk of death. ICU denotes intensive care unit, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

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Table 3. Secondary and Tertiary Outcomes.*

Outcome	Pantoprazole (N=2417)	Placebo (N=2404)	Treatment Effect (95% CI)†	P Value‡
Secondary outcome				
Ventilator-associated pneumonia in ICU — no./total no. (%)§	556/2394 (23.2)	567/2381 (23.8)	1.00 (0.89–1.12)	0.93
Clostridioides difficile infection in hospital — no./total no. (%)	28/2385 (1.2)	16/2377 (0.7)	1.78 (0.96–3.29)	0.50
New renal-replacement therapy in ICU — no./total no. (%)	146/2385 (6.1)	142/2380 (6.0)	1.04 (0.83–1.31)	0.98
Death — no./total no. (%)				
In ICU	488/2402 (20.3)	515/2392 (21.5)	0.98 (0.87–1.11)	0.94
In hospital	630/2399 (26.3)	677/2381 (28.4)	0.96 (0.86–1.07)	0.91
Patient-important upper gastrointestinal bleeding in ICU — no./total no. (%)	36/2385 (1.5)	100/2377 (4.2)	0.36 (0.25–0.53)	<0.001
Tertiary outcome				
Median no. of red-cell units transfused in first 14 days in ICU (IQR)	0 (0–1)	0 (0–1)	0.87 (0.74–1.02)	0.51
Median peak serum creatinine level in ICU (IQR) — μmol/liter	99 (70–190)	99 (69–184)	NA	0.91
Median no. of days of mechanical ventilation (IQR)	6 (3–11)	6 (3–11)	NA	0.73
Median no. of days in ICU (IQR)	10 (6–16)	10 (6–16)	NA	0.48
Median no. of days in hospital (IQR)	20 (11–35)	21 (11–38)	NA	0.47

* To convert the values for creatinine to milligrams per deciliter, divide by 88.4. ICU denotes intensive care unit, IQR interquartile range, and NA not applicable.

† The treatment effect was calculated as a hazard ratio for dichotomous outcomes. A rate ratio is presented for the number of red-cell units transfused because the treatment effect was calculated by means of negative binomial regression. Both measures of treatment effect were adjusted for the prehospital use of a proton-pump inhibitor or H2RA. In addition, mortality analyses were adjusted for the baseline APACHE II score.

‡ P values were corrected for multiplicity with the use of the sequential Holm–Šidák family-wise adjustment.

§ Ventilator-associated pneumonia was defined as a Clinical Pulmonary Infection Score (CPIS) of 6 or more. This score grades 6 domains on a scale from 0 to 2. The score incorporates the quantity and character of tracheal secretions (rare, moderate or large, or mucopurulent), radiographic infiltrates, body temperature, blood leukocyte count and number of band forms, ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, and the presence of pathogenic bacteria.

were the duration of stay in the hospital and in the ICU and hospital mortality.

These results extend research in this field by incorporating a prespecified secondary outcome as defined by ICU survivors and family members.[20] As an outcome, gastrointestinal bleeding that resulted in outcomes that were listed as important to patients and their families occurred more frequently than clinically important bleeding. Our finding that pantoprazole decreased the risk of clinically important upper gastrointestinal bleeding aligns with the results of a previous large trial.[7]

In many populations, proton-pump inhibitors have been associated with initial *C. difficile* infection[29] and an increased risk of recurrence,[30] along with an increased risk of death.[31] However, in our trial, we found no clear difference in the risk of either *C. difficile* infection or ventilator-associated pneumonia between the pantoprazole and placebo groups.[9]

We did not observe an increased risk of death among the most severely ill patients receiving pantoprazole. This finding contrasts with the results of a previous trial that suggested a risk of death in the subgroup of the most seriously ill patients that was greater in the pantoprazole group than in the placebo group.[7,32] Moreover, in a cluster-randomized trial, investigators found that severely ill patients who received pantoprazole had higher mortality than those who received histamine 2–receptor antagonists.[8] We did

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not observe more gastrointestinal bleeding in the subgroup of patients in the placebo group who received prehospital acid suppression, despite concern about rebound gastric acid hypersecretion.[33] Prevailing uncertainty about acid suppression throughout the pandemic and concern about the effect of proton-pump inhibitors on SARS-CoV-2 viral replication[34,35] supported the enrollment of patients with such infection, although no heterogeneity of treatment effect was observed in this subgroup either.

The strengths of this trial include blinded adjudication of all suspected clinically important upper gastrointestinal bleeding in order to apply uniform criteria between adjudicator pairs and across centers for the primary efficacy outcome. Analyses were prespecified, and findings were consistent in unadjusted, adjusted, and sensitivity analyses. The trial incorporated an outcome that was defined according to the ICU experience of patients and their families.[36,37] The enrollment of patients in eight countries enhances the generalizability of the results (Table S13).

Limitations include no patient-reported disability outcomes or data regarding microbiome modification as a mechanism for infection risk.[38] Because there is no universally acknowledged definition of pneumonia,[14] we used the Clinical Pulmonary Infection Score,[39] given the attributable mortality documented in a previous trial.[40] However, the findings were similar when we used other definitions. It is unclear whether these trial results would apply to patients with unassisted breathing.

In our trial, we found that among critically ill patients undergoing invasive mechanical ventilation, the use of pantoprazole resulted in a lower risk of clinically important upper gastrointestinal bleeding than the use of placebo, with no overall effect on mortality.

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APPENDIX

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